A Personal View on Energy, Heat, and Entropy Dissipation in Corneal Tissue

The cornea can be likened to a microcosm. The cornea, the eye's transparent outermost layer, serves as a crucial protective barrier against external stressors such as electromagnetic radiation, pathogens, and desiccation. While appearing macroscopically static and ordered, the cornea is, characteristic of living tissue, metabolically active at the microscopic level. It absorbs oxygen from its external surface and receives nutrients from the aqueous humor of the anterior chamber. This metabolic activity inevitably generates byproducts, which are thought to be eliminated both anteriorly, via the tear film over the epithelial surface, and posteriorly, through the aqueous humor on the endothelial side.

The quantum physicist Erwin Schrödinger, in his seminal work What is Life?, based on lectures delivered in Dublin, introduced thermodynamics to the study of living systems, notably the concept of entropy. He posited that living organisms sustain their internal order by importing "negative entropy" (negentropy) to counteract the natural increase in entropy stemming from their metabolic processes (1). Although "negentropy" remains a debated concept, the second law of thermodynamics—the inherent tendency towards increasing entropy—is universally accepted as applicable to living systems. In this framework, the excretion of waste products can be interpreted as a mechanism for expelling internally generated entropy, analogous to "consuming negentropy" to preserve biological order.

Anatomically, the cornea comprises three primary layers: the superficial epithelium, the intermediate stroma, and the innermost endothelium. These layers are separated by two distinct acellular membranes: Bowman's membrane, between the epithelium and stroma, and Descemet's membrane, between the stroma and endothelium.
The corneal epithelium consists of multiple layers of stratified squamous cells that shield the ocular surface from mechanical, microbial, and environmental insults.
In contrast, the corneal endothelium is a single layer of hexagonal cells in direct contact with the aqueous humor.

Corneal epithelial cells maintain their function and transparency by constantly eliminating from the eye the accumulation of waste molecules and unwanted or mutated antigens resulting from biological activity, along with the associated disorganization of biological information (i.e., an increase in entropy). This elimination occurs through apoptosis, phagocytosis, and tear fluid, and the cells are renewed by a supply from stem cells. In contrast, corneal endothelial cells are non-dividing cells that are arrested in the cell cycle in vivo. Therefore, unlike corneal epithelial cells, they do not expel increased entropy from the eye through a cycle of repeated apoptosis and regeneration.

Within the corneal stroma, continuous energy metabolism generates high-entropy molecules. To maintain homeostasis, a system for expelling these molecules is essential. While autophagy, a recently highlighted intracellular process, contributes to managing cellular waste (primarily by processing internal components rather than expelling them from the cell), the primary

outflow pathways for entropy generated within the cornea are believed to be the tear fluid, conjunctival blood and lymphatic vessels, and, critically, the aqueous humor. Anatomically, the anterior chamber, interfacing with the hexagonally arranged endothelial cells (potentially a manifestation of dissipative structures), is considered the principal route for entropy outflow from the stroma.

Living organisms are generally understood as non-equilibrium open systems, a concept extensively explored by Ilya Prigogine in his theory of dissipative structures (2). This theory describes how, under conditions of thermodynamic entropy dissipation, characteristic self-organizing structures can emerge. This line of thought is further extended by theoretical biologist Stuart Kauffman, who argues that such order is not merely a product of selection but an inherent property of complex systems themselves—a concept he termed "order for free" (3). As prominent examples of dissipative structures, one can point to Bénard convection, where hexagonal convection cells (Bénard cells) spontaneously form under specific conditions, and Bénard-Marangoni convection, which can also produce such hexagonal patterns. The morphology of these cells bears a notable resemblance to the hexagonal arrangement of corneal endothelial cells.

We speculate that a graded, horizontally stratified "High Entropy Zone" (High Entropy-production Zone)—a region of consistently elevated entropy production relative to its surroundings—exists in the anterior corneal stroma, peaking just beneath Bowman’s layer and decaying progressively toward the endothelium. This zone, presumed to have a high density of metabolically active corneal stromal cells, would consequently exhibit relatively high local

temperature and entropy. Radially, the HEZ is higher near the center and lower toward the periphery, forming a gentle in-plane gradient. The existence of this high entropy zone might also be related to a defense mechanism against ultraviolet radiation exposure. The formation of this high entropy zone could be a consequence of the Maximum Entropy Production Principle (MEPP).

This would establish sustained temperature and solute gradients across the corneal stroma. This gradient is hypothesized to induce a convective flow via the Marangoni effect, a phenomenon where differences in surface tension—caused by the gradients in temperature and solute concentration—drive fluid motion. This flow serves as the primary mechanism for driving the dissipation of entropy toward the anterior chamber, thereby maintaining corneal transparency and overall function. These interconnected processes of cellular activity, metabolism, and entropy dissipation within the stroma and endothelium may play pivotal roles in preserving corneal clarity, modulating autoimmune responses (e.g., corneal autoantigen dynamics), influencing corneal transplant immunology, and promoting corneal cell regeneration following injury or disease.

Supporting the concept of dynamic stromal fluid movement, a notable experiment reported by Inoue et al. demonstrated a horizontal, swirling flow of fluorescein dye injected into the corneal stroma (4). This flow of water, moving from the center to the outer parts of the cornea and eventually spreading dye throughout. The pattern of this flow also hinted at a spiral movement in the vertical direction. Significantly, when endothelial cells were damaged by injecting a preservative into the anterior chamber, this migration

ceased, underscoring the necessity of intact endothelial function for this phenomenon. These findings strongly suggest the existence of dynamic water flow within the corneal stroma.

Intriguingly, this water flow pattern closely corresponds to simulations of a hypothesized "High Entropy Zone." While models based on either temperature gradients (thermal Marangoni effect) or solute gradients (solutal Marangoni effect) can reproduce the flow, the solute gradient model appears more physiologically plausible because it depends on the continuous production of metabolic byproducts, a well-documented biological process. Preliminary data support this view, and the simulations provide further support, showing that a model driven solely by a solutal Marangoni effect originating from a "High Entropy Zone" can closely replicate the key metrics of the Inoue et al. experiment. Taken together, this evidence strengthens the physiological plausibility of the HEZ hypothesis as the primary driver of the observed convection.

And the physical forces driving this convection may also influence the structural formation of the adjacent corneal endothelium. Classical Bénard convection alone might not fully account for the high-density hexagonal cell patterns observed in the endothelium under certain conditions. However, it is plausible that Bénard convection (or a Bénard-Marangoni stage dominated by buoyancy) acts as an initial trigger. The resultant temperature and flow fields could then induce and amplify other self-organization mechanisms, particularly surface tension effects (the Marangoni effect), leading to the formation of more stable, high-density hexagonal patterns. Under the theoretical assumption that the corneal endothelial layer is a 5μm liquid layer,

the Marangoni effect could plausibly drive the formation of a dense hexagonal cell population with a density approximating that of the corneal endothelium.

While it is generally accepted that corneal endothelial cells maintain corneal transparency through their Na+/K+ ATPase-mediated pump-leak function, it is also conceivable that convective aspects within the corneal stromal layer and the corneal endothelial layer may contribute to corneal transparency. A recent insightful report also suggests that dissipative structures can form at the nanoscale, implying that entropy dissipation at this scale might contribute to extended interpretations of classical thermodynamic convection models.

We propose that a laminar zone of high entropy is spontaneously and continuously generated in the anterior corneal stroma. To dissipate this entropy towards the anterior chamber, we hypothesize the involvement of convective phenomena analogous to Bénard-Marangoni convection, or an alternative intra-tissue flow initiated by such mechanisms. We further propose that both stromal and endothelial entropy is consistently discharged into the anterior chamber, crucial for maintaining corneal homeostasis. Additionally, the role of the corneal endothelium in facilitating fluid and solute transport, critical for entropy dissipation, is supported by quantitative models of transendothelial fluid dynamics.

Cheng and Pinsky developed enhanced Kedem-Katchalsky equations that account for active ionic transport and fixed charges within the corneal stroma, demonstrating their impact on fluid pressure and osmotic balance across the endothelium (5). Their findings highlight a novel pressure mechanism driven by active ionic fluxes and solvent-solute interactions, which maintains stromal

hydration and corneal transparency. The enhanced K-K equations provide a theoretical framework that links cellular-level active ion transport to pressure and fluid movement. This physical mechanism supports our hypothesis of a convective flow. Driven by the solute gradients from active ion transport, this flow is analogous to solutocapillary Marangoni convection and would facilitate entropy dissipation from the corneal stroma into the anterior chamber, reinforcing the thermodynamic basis of corneal homeostasis.

Recent experiments in electrochemistry have directly demonstrated that ion concentration gradients can induce a powerful solutal Marangoni effect, capable of driving significant fluid dynamics. Park et al. (6) experimentally proved that this Marangoni force, arising from local concentration changes, is strong enough to determine gas bubble dynamics and that its direction depends on the specific anion in the electrolyte. This experimental validation of the solutal Marangoni effect provides strong physical plausibility for its role as a key driving force for the convective flow we hypothesize in the cornea.

The amount of entropy ejected from the endothelial surface (ΔS out) must not be less than the entropy generated within the stroma and endothelium (ΔS in), such that $\Delta S \text{ in} - \Delta S \text{ out} \leq 0$ must always hold. The health and disease of the cornea may be understood as a non-equilibrium open system in which metabolism, structure, fluid dynamics, and thermodynamics all interplay. If this balance is disrupted, the accumulation of waste molecules and the resulting equilibration (loss of order) would lead to corneal cell dysfunction, keratoconus-like microstructural fragility, irreversible corneal damage, corneal allograft rejection, and loss of transparency.

Particularly concerning allogeneic corneal transplantation, this is thought to imply the induction of rejection due to the accumulation of waste denatured allogeneic corneal molecules—which, in other words, suggests that the elimination of these denatured molecules might contribute to the suppression of rejection onset. Efficient entropy dissipation from healthy stromal cells likely promotes similar dissipation from endothelial cells, contributing to the maintenance of endothelial function and the self-organization of corneal tissue. Its validation could pave the way for extending these concepts to include the role of nanoscale dissipative structures, potentially offering new insights into the thermodynamic foundations of corneal tissue homeostasis.

References

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This personal view proposes a new way of understanding corneal function using thermodynamic principles,
but these ideas are theoretical and not yet proven through experiments.

In summary (A personal view)

Core Theoretical Framework

We apply Schrödinger's concept of "negative entropy" (negentropy) to corneal tissue, proposing that:

1. Living corneal tissue generates entropy through metabolic processes
2. Entropy must be continuously expelled to maintain cellular order and function
3. The corneal endothelium is the primary route for entropy dissipation into the anterior chamber, including its own entropy
4. The hexagonal pattern of endothelial cells may represent a dissipative structure optimized for entropy outflow

The Theoretically Definition of the High Entropy Zone (HEZ):

The High Entropy-Production Zone (HEZ) is hypothesized to be a graded, horizontally stratified region in the anterior corneal stroma
that peaks just beneath Bowman’s layer and decays toward the endothelium; radially, it is higher centrally and lower peripherally,
forming a gentle in-plane gradient.

- High metabolic activity generates excess entropy and heat
- Relationship with MEPP
- This creates temperature and solute gradients across the cornea
- Close agreement between HEZ + solutal Marangoni effect and the Inoue et al. experiment in AMR-DNS simulations

Implications for Corneal Maintenance

1. Entropy Balance Equation

We propose that corneal homeostasis requires: ΔS in - ΔS out ≤ 0

Where:

- ΔS in = entropy generated within stroma and endothelium
- ΔS out = entropy expelled through the endothelial surface

When this balance is disrupted (ΔS in > ΔS out):

- Waste molecules accumulate
- Denatured proteins build up
- Loss of cellular order occurs
- Allograft rejection is triggered

2. Novel Therapeutic Approach

The theory suggests that enhancing entropy dissipation could prevent rejection by:

- Facilitating removal of denatured allogeneic proteins (Necessity of antigen clearance)
- Maintaining cellular order in transplanted corneas
- Maintaining and enhancing healthy corneal endothelial cell function

Additional Notes 1:

AMR-DNS simulations based on the HEZ + solutal Marangoni effect may hold the potential
to predict a variety of corneal states with high accuracy.

Additional Notes 2:

Furthermore, to create a comprehensive model of corneal stability, we can define a quantitative risk score,
R, that measures the total deviation from homeostasis by incorporating both entropy and pressure imbalances:

$R = |\Delta S_{in} - \Delta S_{out}| + \lambda |\Delta P - \Delta \Pi_{eq}|$

In this model, $|\Delta P - \Delta \Pi_{eq}|$ represents the imbalance in fluid and osmotic pressures across the endothelium,
and λ is a weighting constant. A higher value of R would indicate a greater disruption of corneal homeostasis.

Additional Notes 3:

The cornea's thermodynamic model may extend to the lens, which can be thought of as the eye's "living crystal."
For perfect transparency, this living crystal must maintain its highly ordered structure against the constant force of entropy (disorder).
When this system fails, the lens may lose its perfect, crystal-like structure, becoming cloudy.

Strengths and Limitations

Strengths:

- Novel thermodynamic framework for understanding corneal physiology
- Integrates multiple scales (cellular, tissue, thermodynamic)
- Provides mechanistic basis for known clinical observations
- Suggests testable hypotheses

Limitations:

- Highly speculative with limited experimental validation
- Entropy quantification in biological systems remains challenging
- Clinical translation would require significant research validation